NDA 17-354/S-042
NDA 17-355/S-044
NDA 17-875/S-030
NDA 17-876/S-029

NOV 24 1999

Parke-Davis Pharmaceuticals
Attention: Ms. Sharon Phillips
Senior Manager, Advertising and Labeling
201 Tabor Road
Morris Plains, NJ 07950

Dear Ms. Phillips:

Please refer to your supplemental new drug applications dated December 22, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Loestrin® Fe 1/20 (norethindrone acetate and ethinyl estradiol Tablets, USP and Ferrous Fumerate tablets), Loestrin® FE 1.5/30 (norethindrone acetate and ethinyl estradiol Tablets, USP and Ferrous Fumerate Tablets), Loestrin® 211.5/30 (norethindrone acetate and ethinyl estradiol), and Loestrin® 211/20 (norethindrone acetate and ethinyl estradiol).

We acknowledge receipt of your submissions dated September 8, and November 16, 1999. Your submission of November 16, 1999 constituted a complete response to our July 20, 1999 approvable letter.

These supplemental new drug applications provide for changes to the label as follows:

CLINICAL PHARMACOLOGY section
Pharmacokinetics subsection

The phannacokinetics of Loestrin have not been characterized; however, the following pharmacokinetic information regarding norethindrone acetate and ethinyl estradiol is taken from the literature.

Absorption
Norethindrone acetate appears to be completely and rapidly deacetylated to norethindrone after oral administration, since the disposition of norethindrone acetate is indistinguishable from that of orally administered norethindrone (1). Norethindrone acetate and ethinyl estradiol are subject to first-pass metabolism after oral dosing, resulting in an absolute bioavailability approximately 64% for norethindrone and 43% for ethinyl estradiol(1-3).

Distribution
Volume of distribution of norethindrone and ethinyl estradiol ranges from 2 to 4 L/kg (1-3). Plasma protein binding of both steroids is extensive (>95%); no norethindrone binds to both albumin and sex hormone binding globulin, whereas etbinyl estra diol binds only to albumin (4).

Metabolism
Norethindrone undergoes extensive biotransformation, primarily via reduction, followed by sulfate and glucuronide conjugation. The majority of metabolites in the circulation are sulfates, with glucuronides accounting for most of the urinary metabolites (5). A small amount of norethindrone acetate is metabolically converted to ethinyl estradiol. Ethinyl Estradiol is also extensively metabolized, both by oxidation and by conjugation with sulfate and glucuronide. Sulfates are the major circulating conjugates of ethinyl estradiol and glucuronides predominate in urine. The primary oxidative metabolite is 2-hydroxy ethinyl estradiol, formed by the CYP3A4 isoform of cytochrome P450. Part of the first-pass metabolism of ethinyl estradiol is believed to occur in gastrointestinal mucosa. Ethinyl estradiol may undergo enterohepatic circulation (6).

Excretion
Norethindrone and ethinyl estradiol are excreted in both urine and feces, primarily as metabolites (5,6). Plasma clearance values for norethindrone and ethinyl estradiol are similar (approximately 0.4 L/hr/kg) (1-3).

Special Populations

Race:
The effect of race on the disposition of Loestrin has not been evaluated.

Renal Insufficiency
The effect of renal disease on the disposition of Loestrin has not been evaluated. In premenopausal women with chronic renal failure undergoing peritoneal dialysis who received multiple doses of an oral contraceptive containing etbinyl estradiol and norethindrone, plasma ethinyl estradiol concentrations were higher and norethindrone concentrations concentrations were unchanged compared to concentrations in premenopausal women with normal renal function.

Hepatic Insufficiency
The effect of hepatic disease on the disposition of Loestrin has not been evaluated. However, etbinyl estradiol and norethindrone may be poorly metabolized in patients with impaired liver function.

Drug-Drug Interactions
Numerous drug-drug interactions have been reported for oral contraceptives. A summary of these is found under PRECAUTIONS, Drug Interactions.

INDICATIONS AND USAGE section
Updated Trussell Table

TABLE I
LOWEST EXPECTED FAILURE RATES DURING THE FIRST YEAR OF CONTINUOUS USE OF METHOD
% of Women Experiencing an Unintended Pregnancy in the First Year of Continuous Use

Method	**Lowest Expected***	**Typical****
(No contraception)	(85)	(85)
Oral contraceptives		3
combined	0.1	N/A***
progestin only	0.5	N/A***
Diaphragm with spermicidal cream or jelly	6	20
Spermicides alone (foam, creams, gels, jellies, vaginal suppositories and vaginal film)	6	26
Vaginal Sponge		
nulliparous	9	20
parous	20	40
Implant	0.05	0.05
Injection: depot medroxyprogesterone acetate	0.3	0.3
IUD		
progesterone T	1.5	2.0
copper T 380 A	0.6	0.8
LN g 20	0.1	0.1
Condom without spermicides		
female	5	21
male	3	14
Cervical Cap with spermacidal cream or jelly		
nulliparous	9	20
parous	26	40
Periodic abstinence (all methods)	1-9	25
Withdrawl	4	19
Female sterilization	0.5	0.5
Male sterilization	0.10	0.15

Adapted from RA Hatcher et al, Reference 7.

* The authors' best guess of the percentage of women expected to experience an accidental pregnancy among couples who initiate a method (not necessarily for the first time) and who use it consistently and correctly during first year if they do not stop for any other reason.
**This term represents "typical" couples who initiate a method (not necessarily for the first time), who experience an accidental pregnancy during the first year if they do not stop use for any other reason.
***N/A - Data not available

PRECAUTIONS section

8. Drug Interactions

Effects of Other Drugs on Oral Contraceptives (78)

Rifampin: Metabolism of both noretbindrone and ethinyl estradiol is increased by rifampin. A reduction in contraceptive effectiveness and increased breakthrough bleeding and menstrual irregularities have been associated with concominant use of rifampin.

Anticonvulsants: Anticonvulsants such as phenobarbital, phenytoin, and carbamazepine, have been shown to increase metabolism of ethinyl estradiol andlor norethindrone, which could result in a reduction in contraceptive effectiveness.

Troglitazone: Administration of troglitazone with an oral contraceptive containing ethinyl estradiol and norethindrone reduced the plasma concentrations of both by approximately 30%, which could result in a reduction of contraceptive effectiveness.

Antibiotics: Pregnancy while taking antibiotics has been reported when the oral contraceptives were administered with antmicrobials such as ampicillan, tetracycline, and griseofulvin. However, clinical pharmacokinetic studies have not demonstrated any consistent effect of antibiotics (other than rifampin) on plasma concentrations of synthetic steroids.

Atorvastatin: Coadminitsration of Atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20%, respectively.

Other: Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol concentrations, possibly by inhibition of conjugation. A reduction in contraceptive effectiveness and increased incidence of breakthrough bleeding has been suggested with phenylbutazone.

Effects of Oral Contraceptives on Other Drugs

Oral contraceptive combinations containing ethinyl estradiol may inhibit the metabolism of other compounds. Increased plasma concentration of cyclosporine, prednisolone, and theophylline have been reported with concomitant administration of oral contraceptives. In addition, oral contraceptives may induce the conjugation of other compounds. Decreased plasma concentrations of acetaminophen and increased clearance of temazepam, salicyclic acid, morphine, and clofibric acid have been noted when these drugs were administered with oral contraceptives.

13. Pediatric Use

Safety and efficacy of Loestrin have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and for users 16 years and older. Use of this product before menarche is not indicated.

REFERENCES section Updated references.

PATIENT PACKAGE INSERT
The Patient Package Insert contained the identical changes listed above.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted November 16, 1999, patient package insert submitted November 16, 1999).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 17-354/S-042, 17-355/S-044, 17-875/S-030, 17-876/S-029." Approval of these submissions by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for these products. All proposed materials should be submitted in draft or mockup form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package inserts directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit acopy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Jennifer Mercier, B.S., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Lisa D. Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research